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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,679	03/11/2005	Thomas Felzmann	4518-0110PUS1	7223

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
11/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,679	FELZMANN, THOMAS	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,13,19 and 21-24* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,19 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's amendment of the claims filed 17 July 2009 has been entered. Applicant's remarks submitted on 17 July 2009 are acknowledged.

Claims 10, 11, 14-18, 20, 25 and 26 are cancelled. Claims 1-9, 12, 13, 19 and 21-24 are pending. Claims 12 and 13 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1-9, 19 and 21-24 are under examination.

Claim Objections/Rejections Withdrawn

The rejection of claims 1, 3-5, 9, 18, 19 and 21-26 under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), is withdrawn in response to Applicant's amendment of the claims to recite wherein said exposure to LPS and IFN-γ occurs over a period of 2-6 hours, however, Bosch teaches a broader window of exposure time, i.e., about 1-24 hours.

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), in view of Asavaroengchai et al. (PNAS, 2002, Jan. 22, Vol. 99:931-936), is withdrawn for reasons set forth above.

The rejection of claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), in view of Rieser (Urol. Int., 1999, Vol. 63(3):151-159), and Felzmann et al. (Cancer Letters, 2000, Vol. 161:241-250, "Felzmann (2000)"), is withdrawn for reasons set forth above.

The rejection of claim 18 under 35 U.S.C. 112, second paragraph, as being indefinite for lacking antecedent basis for the limitation "said active DC", is withdrawn in response to Applicant's cancellation of the claim.

The objection to claim 18 under 37 CFR 1.75 as being a substantial duplicate of claim 1, is withdrawn in response to Applicant's cancellation of the claim.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 9, 19 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1, which was filed as a 371 of PCT/US02/28620, 09/06/2002, and has a provisional filing date on 6 September 2001),

in view of Kalinski et al. (J. Immunol., 1999, Vol. 162:3231-3236, reference provided in the Advisory action mailed on 17 September 2009).

The instant claims are directed to a method for the treatment of a tumor which comprises or consists essentially of administering to a patient in need thereof an effective amount of active dendritic cells (DC) that are tumor-specific and secrete IL-12, said DC being prepared by a process comprising or consisting essentially of: (a) collecting DC or DC precursor cells from a suitable source to obtain a DC culture; (b) loading the DC of said DC culture with a tumor specific antigen, e.g., an antigen from a tumor cell from the patient having said tumor; and (c) exposing said DC culture to a concentration of LPS and a concentration of IFNγ effective to trigger the DC of said DC culture to secrete IL-12, wherein said exposure to LPS and IFNγ occurs over a period of 2-6 hours, e.g., 2 hours, 6 hours (claims 1, 5, 19, 21, 23, 24); wherein the tumor is an advanced malignancy (claim 3); wherein said DC are collected from the patient having said tumor or from a bone marrow donor (claim 4); and wherein the DC have been generated *in vitro* from peripheral blood mononuclear cells (PBMCs) (claim 9); and wherein said active DCs are administered or frozen after exposure to LPS and IFNγ (claim 22).

Bosch teaches that dendritic cells (DCs) are increasingly prepared *ex vivo* for use in immunotherapy, particularly, immunotherapy of cancer [0002]. Bosch teaches a method of preparing DCs *ex vivo* and priming those cells for an antigen-specific cytotoxic T cell response [0010]. Bosch teaches that the method for producing a mature DC population *ex vivo* comprises: (a) providing immature DCs, such as isolating

autologous or allogenic DC precursors and immature DCs from blood (e.g., leukocyte population) and bone marrow [0021] [0029]; and (b) contacting the immature DCs with an effective concentration of IFNγ in combination with an agent that simultaneously provides broad immune stimulation (e.g., BCG, bacille Calmette-Guerin) under culture conditions suitable for maturation of the immature DCs [0010]. Bosch teaches that the immature DCs can be contacted with a predetermined antigen, such as a tumor specific antigen, or a tumor associated antigen (e.g., whole cells, tumor cell lysate, isolated antigens from tumors), prior to or during contacting with BCG and IFNγ [0010] [0044]. Bosch teaches that the mature DC population produces an increased amount of IL-12 [0010]. Bosch teaches that combining IFNγ with certain DC maturation factors, such as bacterial lipopolysaccharide (LPS) and CD40, can also enhance IL-12 production by DCs, as compared to using the factor alone [0006]. Bosch further teaches that the immature DCs are typically contacted with IFNγ and BCG for about 1-24 hours [0040]. Bosch teaches that the mature DCs can be administered to an animal (human or non-human animal) [0019] [0021].

Bosch, however, does not teach that the exposure to LPS and IFNγ occurs over a period of 2-6 hours, e.g., 2 h, 6 h, as recited in claims 1, 19, 21, 23 and 24.

Kalinski et al. teach that DCs at the early stages of maturation (2 h and 4 h) produced elevated amounts of IL-12, and that the ability to produce IL-12 was strongly down-regulated at later time points, e.g., 12 h after the induction of DC maturation (see Abstract). Kalinski et al. teach that while the induction of IL-12 in respnse to LPS in combination with IFNγ was strongly up-regulated in the early stage maturation DCs, the

ability to produce IL-12 was abolished in fully mature DCs (pp. 3233, col. 2, under section "*Mature DC are resistant to the bacterial cytokine inducers, LPS and SAC*", and Fig. 3A, B).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use DCs at the early stages of maturation (e.g., 2 h, 4 h) for cancer immunotherapy. One of ordinary skill in the art would have been motivated to do so, because Bosch teaches that tumor antigen-pulsed, IL-12 secreting DCs are useful for cancer immunotherapy; and Kalinski et al. teach that DCs at the early stages of maturation (especially at 2 h or 4 h) produced higher amounts of IL-12, as compared to fully mature DCs that have lost the ability to produce IL-12. Therefore, the combined teachings provide a reasonable expectation of success for cancer immunotherapy by using the *ex vivo* prepared DCs.

In the remarks filed 17 July 2009, Applicant argues that one of skill would not have found the present invention obvious based on the disclosure of Bosch, because Bosch does not disclose the explicit combination of LPS and IFNγ, nor does Bosch provide data for any maturation period of less than 24 hours or any *in vivo* data. Applicant argues that Bosch discloses that the priming of DCs with IFNγ and BCG causes an increase in IL-12 production over either BCG alone or IFNγ alone. Applicant argues that Bosch suggests 1-24 hour incubation time, but only shows results after 24 hour incubation (Example 1). Applicant argues that the instant specification teaches that cells matured for 24 hours were injected as exhausted DCs, thus, Bosch does not teach

the critical difference between cells matured for 2-6 hours compared to cells matured for 24 hours. Applicant argues that there is no reason to believe that one of skill would change both the maturation factor and the time point, when Bosch teaches that 24 hours is sufficient. Applicant further argues that Bosch does not provide any *in vivo* data, in contrast, Applicant has presented evidence in the specification showing that the results obtained by using the specific method of exposure to LPS and IFNγ for 2-6 hours would be unexpected compared to using different maturation factors, and these results are supported in the Felzmann (2005) paper (of record) and the Felzmann Declaration (of record). Specifically, the "active DCs" which produce IL-12 are therapeutically effective, whereas "exhausted DCs" which "do not produce IL-12 any more" are not effective in a tumor-specific manner *in vivo*. Applicant argues that as Bosch only presents evidence of exhausted DCs (that is, matured for 24 hours with different cytokines), one of skill would have no way to predict that the claimed method would be at least 3 times or 5 times as effective as the method Bosch actually suggests, thus, any *prima facie* case of obviousness is overcome in view of the evidence of unexpected results shown by the specification and the Felzmarm Declaration.

Applicant's arguments have been considered, but are not sufficient to overcome the rejection as being unpatentable over Bosch, in view of Kalinski et al., as set forth above.

Bosch teaches that combining IFNγ with certain DC maturation factors, such as bacterial LPS or CD40, can enhance IL-12 production by DCs, as compared to use the factor alone [0006], thus, Bosch clearly suggests the combination of LPS and IFNγ for

enhancing IL-12 production by DCs. Even though Bosch states that the signal transduction pathways in human monocyte-derived dendritic cells and the mechanism for IFNγ action in these cells have not been established [0006], one of ordinary skill in the art would still have found it obvious to use the combination of LPS and IFNγ because Bosch teaches that this combination has been demonstrated to be able to increase IL-12 production by DCs.

With regard to the maturation time, in particular, 2-6 h, Kalinski et al. have provided experimental data showing that DCs at the early stages of maturation (2 h and 4 h) produced the highest amounts of IL-12, and that the ability to produce IL-12 was strongly down-regulated at later time points (e.g., 12 h) after the induction of DC maturation (see Abstract). Kalinski et al. showed that while the induction of IL-12 in respnse to a combination of LPS and IFNγ was strongly up-regulated in the early stage maturation DCs, the ability to produce IL-12 was abolished in fully mature DCs (pp. 3233, col. 2, and Fig. 3A, B). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to use DCs at the early stages of maturation (e.g., 2 h, 4 h), because Kalinski et al. clearly teach the difference between the DCs at the early stages of maturation as “active DCs" that prodice an increased amount of IL-12 production, and the DCs at later time points (e.g., 12 h) after the induction of maturation as “exhaused DCs”, in which the ability to produce IL-12 was strongly down-regulated or even abolished.

With respect to the unexpected results presented in the specification, and in the supporting evidence presented previously (the Felzmann (2005) paper and the

Felzmann Declaration), the data shown in the Kalinski et al. reference indiactes that the amount of IL-12 produced by DCs at different matruartion stages vary dramatially, i.e., more than 3-fold or 5-fold difference, for example, comparing 4 h time point and 12 h time points (pp. 3233, Fig. 2). Furthermore, the difference of IL-12 production between the early stage maturation DCs and mature DCs treated with LPS and IFNγ was even more dramatic (more than 100-fold) (pp. 3234, Fig. 3B). Thus, based on such a large quantitative difference in the amount of IL-12 produced, one of ordinary skill in the art would expect that the DCs at the early stages of maturation (e.g., 2 h and 4 h) have higher bioactivity since these cells produce much higher amount of IL-12 than the later stage maturation DCs. Also, in the Kalinski et al.'s study, they compared IL-12 production induced by difference IFNγ combinations, e.g., CD40L/IFNγ, LPS/IFNγ, and SAC/IFNγ, the dats shown in Fig. 3B clearly suggests that although both LPS and SAC are bacterial proteins, LPS/IFNγ is more effective than the other bacteria protien SAC. This results further provide motivation to use the combination of LPS/IFNγ.

For these reasons, the instant claims are *prima facie* obvious in view of the teachings of Bosch and Kalinski et al.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), in view of Kalinski et al., as applied to claims 1, 3-5, 9, 19 and 21-24 above, and further in view of Asavaroengchai et al. (PNAS, 2002, Jan. 22, Vol. 99:931-936, reference provided previously).

Bosch and Kalinski et al. teach as set forth above. These references, however, do not teach that the treatment is performed after bone marrow transplantation (claim 2).

Asavaroengchai et al. teach that bone marrow transplants (BMT) or peripheral stem cell transplants are currently being used for the treatment of hematopoietic and solid tumors, and combining suitable immunization approaches with BMT can overcome tumor induced defects in the host anti-tumor immune response. Asavaroengchai et al. teach that in a therapeutic setting, tumor antigen-pulsed DCs can have an impact on residual tumor that remains following BMT (pp. 931, see Abstract and Introduction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bosch and Kalinski et al. with those of Asavaroengchai et al., to perform the treatment after bone marrow transplantation. One of ordinary skill in the art would have been motivated to do so, because Bosch teaches a method of cancer immunotherapy by using tumor antigen-pulsed DCs that release IL-12 upon maturation with LPS and IFNγ; Kalinski et al. further teach an optimal maturation stages (e.g., 2h, 4 h) when the DCs produce an elevated amount of IL-12; and Asavaroengchai et al. furthermore teach that tumor antigen-pulsed DCs can have impact on residual tumor that remains following BMT. Therefore, the combined teachings provide a reasonable expectation of successfully treating a tumor in a patient.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), in view of Kalinski et al., as applied to claims 1, 3-5, 9, 19 and 21-24 above, and further in view of Rieser (Urol. Int., 1999, Vol. 63(3):151-159), and Felzmann et al. (Cancer Letters, 2000, Vol. 161:241-250, "Felzmann (2000)") (both references provided previously).

Bosch and Kalinski et al. teach as set forth above. These references, however, do not teach that the DCs are additionally charged with a tracer antigen (claim 6) that is keyhole limpet hemocyanine (KLH) (claim 7), or additionally charged with an adjuvant tetanus toxoid (claim 8).

Rieser teaches using KLH as a tracer molecule for the determination of the magnitude, kinetics, and T-helper type-1 bias of the cellular and humoral immune response induced by DC-based immunization (pp. 151, see Abstract).

Felzmann (2000) further teaches Xenogenization by tetanus toxoid (TT) loading into human tumor cells for anti-tumor immune therapy (pp. 241, Abstract). Felzmann (2000) teaches that unresponsiveness to tumor associated antigens (TAAs) could be overcome when a mixture of TAAs was used together with class II restricted peptides from TT for cell pulsing *in vitro* (pp. 241, Introduction, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bosch and Kalinski et al. with those of Rieser and Felzmann (2000), to additionally load DCs with a tracer antigen, e.g., KLH, and an adjuvant tetanus toxoid. One of ordinary skill in the art would have been motivated to do so, because Bosch teaches a method of cancer immunotherapy

by using tumor antigen-pulsed DCs that release IL-12 upon maturation with LPS and IFNγ; Kalinski et al. further teach an optimal maturation stages (e.g., 2h, 4 h) when the DCs produce an elevated amount of IL-12; and Rieser and Felzmann (2000) furthermore teach using KLH as a tracer molecule for determination of the kinetics of the immune therapy, using tetanus toxoid (TT) to overcome unresponsiveness to TAAs. Therefore, the combined teachings provide a reasonable expectation of successfully treating a tumor in a patient.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Xiaozhen Xie/
Xiaozhen Xie, Ph.D.
November 4, 2009